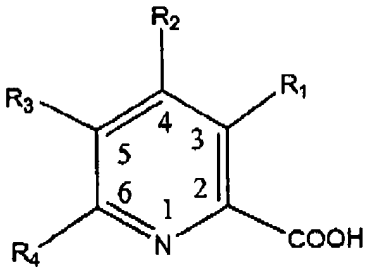

or a pharmacologically acceptable salt thereof,

wherein R_1, R_2, R_3, or R_4 are independently selected from the group consisting of a carboxyl group, methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, secondary butyl group, tertiary butyl group, pentyl group, isopentyl group, neopentyl group, fluorine, chlorine, bromine, iodine, and hydrogen.

C13

110. (New) A method of controlling replication of a virus comprising contacting a cell with the composition of claim 109.

111. (New) The method of claim 110, wherein the virus is a hepatitis C virus.

REMARKS

Claims 13-53 and 65-111 are pending in the application. Claims 13-22, 24, 28-30, 32-34, 38-40 and 43-83 are rejected. Claims 23, 25-27, 31, 25-37, 41 and 42 are objected to. Claims 84-111 have been added. Claims 54-64 have been cancelled.

Claims 13, 18, 21, 39, 43, 47, 48, 59, 63, 69, 70, 74, 75, 78, 79 and 83 are rejected under 35 U.S.C. § 112, first paragraph, as based on a disclosure that is not enabling, and as containing subject matter that was not sufficiently described in the specification. The Examiner argues that "a peptide of sixteen amino acids" is critical to the practice of the invention, but are not included in the claims and are not enabled or described by the disclosure. The phrase "a peptide of sixteen amino acids" has been removed from the claims. As such, Applicants submit that claims are fully enabled and sufficiently described in the specification in accordance with 35 U.S.C. § 112, first paragraph. Accordingly, Applicants

respectfully request that the rejection of claims 13, 18, 21, 39, 43, 47, 48, 59, 63, 69, 70, 74, 75, 78, 79 and 83 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 79, 81 and 83 are rejected under 35 U.S.C. §112, second paragraph. The Examiner argues that the term "contacting" renders the claims indefinite. The Examiner believes that it is unclear if the two ingredients are physically contacted with each other or if they are reacted together, thus causing a chemical reaction. In response, claims 79, 81 and 83, have been amended to clarify that the item to be preserved is physically contacted with a composition comprising the claimed metal chelating agent. Therefore, Applicants submit that claims 79, 81 and 83 are sufficiently definite under 35 U.S.C. §112, second paragraph.

With regard to claim 81, the Examiner argues that the claim reads on 0%, and therefore, is vague and indefinite. Claim 81 has been amended to clarify that the composition of claim 79 comprises the claimed metal ion chelating agent, but in a concentration of less than about 0.025% by weight. As such, the claim clearly does not read on 0% and must comprise the claimed metal ion chelating agent, according to the claim language. Accordingly, it is submitted that claim 81, as amended, is not vague or indefinite.

For all of the above reasons, it is submitted that claims 79, 81 and 83 are sufficiently definite and in accordance with 35 U.S.C. §112, second paragraph. Accordingly, Applicants respectfully request that the rejection of claims 79, 81 and 83 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claims 13, 18, 21, 39, 43, 47, 48, 53, 54, 58, 59, 63, 69, 70, 74, 75, 78, 79 and 83 are rejected under 35 U.S.C. §112, second paragraph. The Examiner maintains that the claims are indefinite because the applicants failed to specify a list of amino acids, or their configurations, which he intends to encompass in the broad terminology "a peptide of sixteen amino acids."

Applicant traverses the rejection. The claims have been amended to remove the terminology. Therefore, Applicants respectfully request that the rejection of claims 13, 18, 21, 39, 43, 47, 48, 53, 54, 58, 59, 63, 69, 70, 74, 75, 78, 79 and 83 under 35 U.S.C. §112, second paragraph be withdrawn.

Claims 13-22, 24, 28-30, 32-34, 38-40, 43-74 are rejected under 35 U.S.C. §102(b) as being anticipated by Otsu et al. The Examiner argues that Otsu et al. teaches picolinic acids according to formula I, metal salts and derivatives according to the formula, and amino acid and peptide derivatives of the formula. It is argued that Otsu et al. reads on any metal salt of the instant claimed picolinic acid, not just zinc salts. Applicant traverses the rejection.

Otsu et al. describes a method of suppressing the production of sunburn cells, a method of inducing metallothionein, a method of treating skin diseases and a method of screening UV rays by the administration of an effective amount of a zinc salt, zinc complex, or salt of a zinc complex of a compound selected from the group consisting of nicotinamides, picolinamides, 3,4-dihydroxybenzoic acids, amino acids, peptides, hinokitiols and certain pyridine carboxylic acids. Otsu et al., Abstract; Otsu et al., col. 2, lines 42-57. Otsu et al. describes methods of suppressing the production of sunburn cells, inducing metallothionein, treating skin diseases and screening UV rays by *introducing* chelated zinc into infected cells to increase the zinc, and MT activity within the cells. Otsu et al., col. 2, lines 42-57. Otsu et al. does not teach the use of picolinic acid or its derivatives to *remove* zinc from cells. Otsu et al., col. 2, lines 42-57. Zinc complexes, zinc salts and complexes thereof are used simply as means by which zinc is introduced into infected cells. Otsu et al., col. 2, lines 42-57. According to the method of Otsu et al., metallothioneins (MT) are induced by zinc. Otsu et al., col. 2, lines 42-57. Otsu et al. teaches that MT functions as a scavenger of free radicals, which are generated at the onset of

inflammations. Otsu et al., col. 2, lines 42-57. In dermatological inflammations caused by external irritative stimulants, such as sunburn or the like, MT could act to quench the free radicals released from leukocytes and thereby exhibit an anti-oxidation action to diminish cell damage, to activate the immune system, and to further prevent the accelerated aging of the skin. Otsu et al., col. 2, lines 42-57. Accordingly, Otsu et al. teaches the administration of zinc for inducing MT to be present, or to increase MT in the epidermal keratinous layer of the skin to suppress the formation of sunburn cells. Otsu et al., col. 2, lines 42-57. It is the activity of the zinc that results in the defense against sunburn and other dermatological inflammations. Otsu et al., col. 2, lines 42-57.

Alternatively, claims 13-22, 24, 28-30, 32-34, 38-40, 43-47, are directed to compositions or preparations comprising fusaric acid, or pharmacologically acceptable salts thereof, other than zinc picolinate, and uses thereof to treat various conditions by denaturing infected cells by chelating or removing zinc and other metals within the metal-protein complexes of those cells. As was acknowledged by the Examiner in a telephone conversation on April 18, 2003, Otsu et al. is not directed to methods or compositions that do not employ zinc complexes, zinc salts, or salts of zinc complexes.

Claims 13-22, 24, 28-30, 32-34, 38-40, 43-74 are directed to compositions or preparations comprising fusaric acid and salts thereof other than zinc picolinate, and uses thereof in the treatment of various conditions. Unlike the compositions and methods described in Otsu et al., the compositions and methods of claims 13-22, 24, 28-30, 32-34, 38-40, 43-47 are not directed to, and do not utilize zinc complexes, zinc salts, or salts of zinc complexes to introduce zinc into infected cells. Therefore, one looking to the methods of Otsu et al. would add zinc to

the infected cells, and would not be motivated to inactivate zinc-complexes by chelating or removing metal from the viral protein, which is the mode of action of the present invention.

Claim 13 is not anticipated by Otsu et al. Claim 13 is directed to pharmacologically active picolinic acid, salts and claimed derivatives thereof, other than zinc picolinate. The compound of the claimed invention is clearly not taught by Otsu et al. The claimed compounds treat diseases, disorders and conditions by *chelating* or *removing* zinc or other metals within a metal-protein complex of an infected cell, thereby denaturing the protein complex within the cell and disrupting viral proteins within the cell. Otsu et al. does not teach or describe picolinic acid, fusaric acid, pharmacologically acceptable salts or derivatives thereof that act by the same mechanism. Otsu et al. describes methods of suppressing the production of sunburn cells, inducing MT, treating skin diseases and screening UV rays by *introducing* chelated zinc into infected cells to increase the zinc concentration, and MT activity within the cells. Otsu et al., col. 2, lines 42-57. In addition, Otsu et al. does not describe picolinic acid and/or fusaric acid, pharmacologically acceptable salts, or derivatives therefore other than zinc picolinate. Zinc complexes, zinc salts and complexes thereof are used simply as means by which zinc is introduced into infected cells. Otsu et al., col. 2, lines 42-57. It is the activity of the zinc that results in the defense against sunburn and other dermatological inflammations. Otsu et al., col. 2, lines 42-57. The claimed compounds act to remove zinc. Accordingly, amended claim 13 is not anticipated by Otsu et al., and it is respectfully requested that the rejection of amended claim 13 under 35 U.S.C. §102(b) be withdrawn.

Claims 14-17 depend from amended claim 13, and therefore incorporate all of the subject matter therein. Since it is submitted for the aforementioned reasons that amended claim 13 is patentable over Otsu et al., it is likewise submitted that claims 14-17 are patentable over Otsu et

al. for the same reasons. Therefore, it is respectfully requested that the rejection of claims 14-17 under 35 U.S.C. §102(b) be withdrawn.

Claim 18, as amended, is not anticipated by Otsu et al. Claim 18 is directed to pharmacologically active fusaric acid and stated derivatives thereof. Otsu et al. does not describe fusaric acid adapted for the treatment of hepatitis C infections, angiogenesis, sunburn, metastatic colon cancer and upper respiratory infections, wherein the disease, disorder or condition is mediated by a protein having a metal ion-protein complex. Nowhere in Otsu et al. is the use of fusaric acid discussed. In fact, Otsu et al. teaches methods which involve the introduction of zinc into cells, which is not the mode of action of the claimed compositions. Accordingly, amended claim 18 is not anticipated by Otsu et al. and it is respectfully requested that the rejection of amended claim 18 under 35 U.S.C. §102(b) be withdrawn.

Claims 19 and 20 depend from amended claim 18, and therefore incorporate all of the limitations therein. Since it is submitted for the aforementioned reasons that claim 18 is patentable over Otsu et al., it is likewise submitted that claims 19 and 20 are patentable over Otsu et al. for the same reasons. Therefore, it is respectfully requested that the rejection of claims 19 and 20 under 35 U.S.C. §102(b) be withdrawn.

Claim 21, as amended, is directed to a method for treating metastatic colon cancer, hepatitis C infections, angiogenesis, sunburn, or upper respiratory infections comprising administering an effective amount of picolinic acid, fusaric acid, pharmacologically acceptable salts or claimed derivatives thereof to an individual having metastatic colon cancer, hepatitis C infections, angiogenesis, sunburn, or upper respiratory infections, wherein when said method is for the treatment of sunburn the agent is not zinc picolinate. Otsu et al. does not describe the claimed methods. Nowhere in Otsu et al. is the use of fusaric acid or picolinic acid to treat

metastatic colon cancer, hepatitis C infections, angiogenesis, sunburn, or upper respiratory infections described. Although Otsu et al. describes methods of suppressing the production of sunburn cells by the administration of zinc picolinate, methods of treating sunburn using picolinic acid, fusaric acid and claimed derivatives thereof are not described or suggested.

Further, the claimed methods involve the treatment of diseases, disorders and conditions by *chelating* or *removing* zinc or other metals within a metal-protein complex of an infected cell, thereby denaturing the protein complex within the cell and disrupting viral proteins within the cell. Otsu et al. does not teach or describe methods that act by the same mechanism. Otsu et al. describes methods that involve the *introduction* of chelated zinc into infected cells to increase the zinc concentration, and MT activity within the cells. Otsu et al., col. 2, lines 42-57. Zinc complexes, zinc salts and complexes thereof are used simply as means by which zinc is introduced into infected cells. Otsu et al., col. 2, lines 42-57. It is the activity of the zinc that results in the defense against sunburn and other dermatological inflammations. Otsu et al., col. 2, lines 42-57. This is not the mechanism of action of the claimed methods. Accordingly, amended claim 21 is not anticipated by Otsu et al., and it is respectfully requested that the rejection of claim 21 under 35 U.S.C. §102(b) be withdrawn.

Claims 22-38 depend either directly or indirectly from amended claim 21, and therefore incorporate all of the subject matter therein. Since it is submitted for the aforementioned reasons that amended claim 21 is patentable over Otsu et al., it is likewise submitted that claims 22-38 are patentable over Otsu et al. for the same reasons. Therefore, it is respectfully requested that the rejection of claims 22-38 under 35 U.S.C. §102(b) be withdrawn.

Claim 39, as amended, is directed to a method for the treatment f diseases comprising administering an effective amount of fusaric acid or pharmacologically acceptable salts or

derivatives thereof to an individual having metastatic colon cancer, hepatitis C infections, angiogenesis, sunburn, or an upper respiratory infection. Otsu et al. does not describe methods for the treatment of hepatitis C infections, angiogenesis, sunburn, metastatic colon cancer or upper respiratory infections by the administration of fusaric acid. Rather, Otsu et al. describes methods of suppressing the production of sunburn cells, inducing metallothionein, treating skin diseases and screening UV rays by the administration of an effective amount of zinc picolinate. Nowhere in Otsu et al. is the use of fusaric acid to treat metastatic colon cancer, hepatitis C infections, angiogenesis, sunburn, or upper respiratory infections discussed. Further, Otsu et al. teaches the introduction of zinc to the infected cells to treat certain conditions. The claimed methods involve the removal of zinc from metal-protein complexes to treat the stated diseases, disorders and conditions. Claim 39, as amended, is not directed to and does not encompass methods for treating sunburn by the administration of zinc picolinate. Accordingly, amended claim 39 is not anticipated by Otsu et al., and it is respectfully requested that the rejection of claim 39 under 35 U.S.C. §102(b) be withdrawn.

Claims 40-42 depend from amended claim 39, and therefore incorporate all of the subject matter therein. Since it is submitted for the aforementioned reasons that amended claim 39 is patentable over Otsu et al., it is likewise submitted that claims 40-42 are patentable over Otsu et al. for the same reasons. Therefore, it is respectfully requested that the rejection of claims 40-42 under 35 U.S.C. §102(b) be withdrawn.

Claim 43, as amended, is directed to a systemic preparation comprising approximately 1% to approximately 100% fusaric acid, picolinic acid, or a pharmacologically acceptable salt or a claimed derivative thereof and a pharmacologically acceptable carrier, wherein the preparation does not comprise zinc picolinate. Otsu et al. does not describe systemic preparations

comprising fusaric acid, picolinic acid, or a pharmacologically acceptable salt or derivative thereof, other than zinc picolinate. Rather, Otsu et al. describes methods of suppressing the production of sunburn cells, inducing metallothionein, treating skin diseases and screening UV rays by the administration of an effective amount of zinc picolinate. Nowhere in Otsu et al. is the use of fusaric acid, picolinic acid, or a pharmacologically acceptable salt or derivative thereof, other than zinc picolinate, in a systemic preparation described. Claim 43, as amended, is not directed to a systemic preparation comprising zinc picolinate. In addition, for the reasons stated above, the methods of Otsu et al. do not involve the removal of zinc from metal-protein complexes. Rather, Otsu et al. teaches the introduction of zinc into cells for the treatment of disease. Accordingly, amended claim 43 is not anticipated by Otsu et al. Therefore, it is respectfully requested that the rejection of claim 43 under 35 U.S.C. §102(b) be withdrawn.

Claims 44-46 depend from amended claim 43, and therefore incorporate all of the subject matter therein. Since it is submitted for the aforementioned reasons that amended claim 43 is patentable over Otsu et al., it is likewise submitted that claims 44-46 are patentable over Otsu et al., and it is respectfully requested that the rejection of claims 44-46 under 35 U.S.C. §102(b) be withdrawn.

Claim 47 is directed to a systemic preparation comprising approximately 1% to approximately 100% fusaric acid or a pharmacologically acceptable salt or claimed derivative thereof and a pharmacologically acceptable route of administration. Otsu et al. does not describe systemic preparations comprising fusaric acid or a pharmacologically acceptable salt or a claimed derivative thereof. Rather, Otsu et al. describes methods of suppressing the production of sunburn cells, inducing metallothionein, treating skin diseases and screening UV rays by the administration of an effective amount of zinc picolinate. Nowhere in Otsu et al. is the use of

fusaric acid in a systemic preparation described. Claim 47, as amended, is not directed to a systemic preparation comprising zinc picolinate, or a derivative thereof. Accordingly, amended claim 47 is not anticipated by Otsu et al., and, it is respectfully requested that the rejection of claim 47 under 35 U.S.C. §102(b) be withdrawn.

Claim 48, as amended, is directed to an intranasal solution comprising about 0.01mM to about 50mM fusaric acid, picolinic acid, or a pharmacologically acceptable salt or derivative thereof and at least one nebulizing agent, wherein the intranasal solution does not comprise zinc picolinate. Otsu et al. does not describe intranasal solutions comprising fusaric acid, picolinic acid, or a pharmacologically acceptable salt or derivative thereof, other than zinc picolinate. Rather, Otsu et al. describes methods of suppressing the production of sunburn cells, inducing metallothionein, treating skin diseases and screening UV rays by the administration of an effective amount of a zinc picolinate to increase the zinc concentration, thereby inducing MT. In addition, nowhere in Otsu et al. is the use of fusaric acid or picolinic acid in an intranasal solution described. Claim 48, as amended, is not directed to an intranasal solution comprising zinc picolinate. Further, as discussed above Otsu et al. teaches the introduction of zinc for the treatment of disease, which is not the mode of action for the claimed compositions. Accordingly, amended claim 48 is not anticipated by Otsu et al., and it is respectfully requested that the rejection of claim 48 under 35 U.S.C. §102(b) be withdrawn.

Claims 49-52 depend from amended claim 48, and therefore incorporate all of the subject matter therein. Since it is submitted for the aforementioned reasons that amended claim 48 is patentable over Otsu et al., it is likewise submitted that claims 49-52 are patentable over Otsu et al. for the same reasons. Therefore, it is respectfully requested that the rejection of claims 49-52 under 35 U.S.C. §102(b) be withdrawn.

Claim 53 is directed to an intranasal solution comprising about 0.01mM to about 50mM fusaric acid or a pharmacologically acceptable salt, or claimed derivative thereof and at least one nebulizing agent. Otsu et al. does not describe intranasal solutions comprising fusaric acid or a pharmacologically acceptable salts, or claimed derivatives thereof. Rather, Otsu et al. describes methods of suppressing the production of sunburn cells, inducing metallothionein, treating skin diseases and screening UV rays by the administration of an effective amount of a zinc picolinate. Claim 53 is not directed to an intranasal solution comprising zinc picolinate. Accordingly, claim 53 is not anticipated by Otsu et al., and it is respectfully requested that the rejection of claim 53 under 35 U.S.C. §102(b) be withdrawn.

Claims 54-57 have been canceled. Therefore, it is respectfully requested that the rejection of claims 54-57 under 35 U.S.C. §102(b) be withdrawn.

Claims 58-64 have been cancelled. Therefore, it is respectfully requested that the rejection of claims 58-64 under 35 U.S.C. §102(b) be withdrawn.

Claim 65, as amended, is directed to an ophthalmic preparation for the control of angiogenesis comprising about 0.01% to about 99% fusaric acid, picolinic acid, or a pharmacologically acceptable salt thereof, and a pharmacologically acceptable carrier. Otsu et al. does not describe ophthalmic preparations comprising about 0.01% to about 99% fusaric acid, picolinic acid, or a pharmacologically acceptable salt thereof, and a pharmacologically acceptable carrier. Rather, Otsu et al. describes methods of suppressing the production of sunburn cells, inducing metallothionein, treating skin diseases and screening UV rays by the administration of an effective amount of zinc picolinate, or other zinc complex, zinc salt, or salt of a zinc complex. Nowhere in Otsu et al. is the use of an ophthalmic preparation described. Further, Otsu et al. teaches the introduction of zinc to treat disease, which is not the mode of

action of the claimed compositions. Accordingly, amended claim 65 is not anticipated by Otsu et al., and it is respectfully requested that the rejection of amended claim 65 under 35 U.S.C. §102(b) be withdrawn.

Claims 66-68 depend from amended claim 65, and therefore incorporate all of the subject matter therein. Since it is submitted for the aforementioned reasons that amended claim 65 is patentable over Otsu et al., it is likewise submitted that claims 66-68 are patentable over Otsu et al. for the same reasons. Therefore, it is respectfully requested that the rejection of claims 66-68 under 35 U.S.C. §102(b) be withdrawn.

Claim 70, as amended, is directed to a lavage comprising fusaric acid, picolinic acid, or a pharmacologically acceptable salt thereof. Otsu et al. does not describe lavages comprising fusaric acid, picolinic acid, or salts thereof. Nowhere in Otsu et al. are lavages described. Accordingly, amended claim 70 is not anticipated by Otsu et al., and it is respectfully requested that the rejection of amended claim 70 under 35 U.S.C. §102(b) be withdrawn.

Claims 71-73 depend from amended claim 70, and therefore incorporate all of the subject matter therein. Since it is submitted for the aforementioned reasons that amended claim 70 is patentable over Otsu et al., it is likewise submitted that claims 71-73 are patentable over Otsu et al. for the same reasons. Therefore, it is respectfully requested that the rejection of claims 71-73 under 35 U.S.C. §102(b) be withdrawn.

Claim 74, as amended, is directed to a lavage comprising fusaric acid, or a pharmacologically acceptable salt thereof. Otsu et al. does not describe lavages comprising fusaric acid. Rather, Otsu et al. describes methods of suppressing the production of sunburn cells, inducing metallothionein, treating skin diseases and screening UV rays by the administration of an effective amount of zinc picolinate. Nowhere in Otsu et al. is the use of

fusaric acid, or salts thereof, described. Accordingly, amended claim 74 is not anticipated by Otsu et al. Therefore, it is respectfully requested that the rejection of amended claim 74 under 35 U.S.C. §102(b) be withdrawn.

Claims 71-73, 76, 77, 80 and 82 are rejected under 35 U.S.C. §112 as being dependent on rejected indefinite base claims. Claims 71-73, 76, 77, 80 and 82 are dependent upon claims 70, 75, 79 and 81, which are submitted to be patentable for the aforementioned reasons. As such, Applicants submit that the claims are no longer dependent upon rejected base claims, and respectfully requests that the rejection of claims 71-73, 76, 77, 80 and 82 under 35 U.S.C. §112 be withdrawn.

For all of the above reasons, it is submitted that all of the claims, as amended, are patentable over Otsu et al. Therefore, Applicant respectfully requests that the rejection of claims 13-22, 24, 28-30, 32-34, 38-40, 43-74 under 35 U.S.C. §102(b) be withdrawn.

Claims 84-111 have been added. Claims 84-111 are submitted to be patentable over Otsu et al. Claims 84-111 are directed to the use of compositions comprising picolinic acid and/or fusaric acid, and pharmacologically effective salts and claimed derivatives thereof for the treatment of certain diseases. The compositions work by chelating or removing zinc from metal-protein complexes , thereby denaturing the protein and treating the condition. Otsu et al. is directed to the treatment of certain diseases by the introduction of zinc into cells, which is not the mode of action for the methods and compositions of claims 84-111.

Applicant believes that the arguments asserted and the amendment presented herein place the application in condition for allowance. If the present amendments and arguments do not place the application in condition for allowance, the Examiner is respectfully requested to contact the Applicant's undersigned attorney by telephone at (314) 552-6123.

Respectfully submitted,
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Enclosures: Amended Claims Sheet
Pending Claims sheet

Cc: Avinash Amin (w/ encl.)